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(71)(72) Applicants and Inventors: ANDREASSEN, Troels, Torp [DK/DK]; Skodshøjen 9, DK-8249 Risskov (DK). JØRGENSEN, Jørgen, Peter, Holmberg [DK/DK]; Engdalgårdsvej 6, DK-8330 Beder (DK). BAK, Bue, Kruse [DK/DK]; Hovmarksvej 154, DK-8700 Horsens (DK).

(74) Agent: NOVO NORDISK A/S; Patent Department, Novo Allé, DK-2880 Bagsvaerd (DK).

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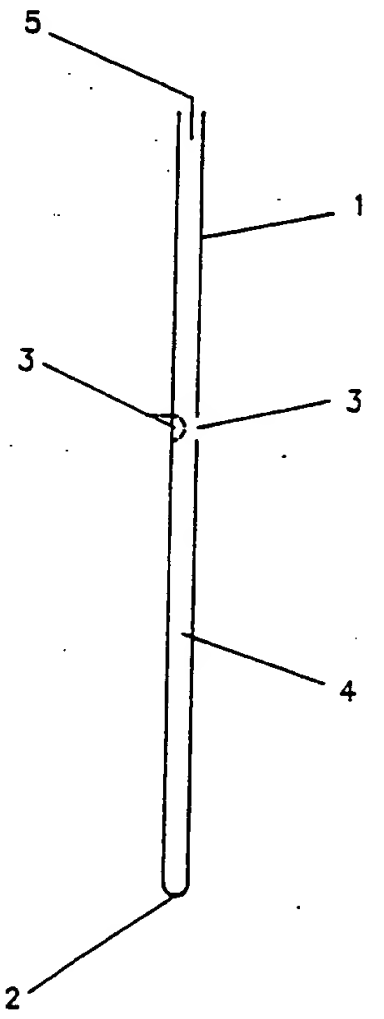
*With amended claims.*

(54) Title: A METHOD AND DEVICE FOR LOCAL ADMINISTRATION OF BIOLOGICALLY ACTIVE SUBSTANCES

(57) Abstract

The invention relates to a method for local administration of biologically active substance(s) enhancing the healing of bone fractures or of a bone and a prosthesis to be united directly to the bone surfaces to be healed or the interface between a bone and a prosthesis which are to be united, and a device and an agent for use in such a method. Furthermore, the use of human growth hormone, thyroid hormone, antibiotic(s) and/or local growth factors for the preparation of a pharmaceutical preparation for enhancing the healing of bone fractures or of a bone and a prosthesis to be united is described.



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TITLE

A Method and Device for Local Administration of Biologically Active Substances.

The present invention relates to a method for local administration of biologically active substances enhancing the healing of bone fractures or of a bone and a prosthesis to be united and a device which can be used carrying out the method. Furthermore, the invention relates to an agent for use for local administration for enhancing the healing bone fractures or of a bone and a prosthesis to be united and to the use of human growth hormone, thyroid hormone, growth factors, morphogens, cell growth stimulants and/or antibiotic(s) for this purpose.

## BACKGROUND OF THE INVENTION

Bone formation, healing of fractures, and healing of prostheses such as joint prostheses are depending on basal biological processes which seem to be related. These processes which have not yet been explained in detail are being studied intensively, partly to understand the biological correlations, and partly to develop "biological tools" enabling influencing or stimulating the processes of healing.

Materials of prostheses and materials and principles of osteosynthesis have been undergoing a drastic development aiming at adapting the mechanical properties of the materials to the demands of the human bone, offering suitable patterns of load and increasing the biocompatibility (e.g. by reducing the liberation of ions from the materials).

Even though the d v lopment of design of prostheses and materials f steosynthesis will proceed it is cl ar that "biological tools" will be absolutely necessary in the future bone surgery as the biological processes are hampered by a number of conditions as well as in elderly people. In these cases even the most advanced design of materials will not be sufficient. When inserting prostheses having high loading, especially hip joints, knee joints, or ankle joints is is crucial to have a very quick inset of healing and a rapid development of strength as it is essential for the patients to avoid confinement to bed as early as possible in order to avoid thrombosis. At the same time is essential to avoid movements of the parts to be united in the first period after the operation in order to avoid the formation of fibrous tissue around the prosthesis reducing the binding strength and thus increasing the risk that the prosthesis will work loose. Such working loose now often implies that the prosthesis has become loose after 5 to 15 years.

There is a wish to avoid using bone cement when implanting prostheses such as hip joints as all the old bone cement must be removed from the internal of the bone in case a prosthesis is to be replaced due to working loose. Thus it is tried to adapt the bone parts to have a press fit with the prosthesis in order to avoid the use of bone cement, and it has been proposed to provide the prosthesis with a coating of porous metal, titanium fiber mesh and/or hydroxyapatite in order to have a better bony ingrowth for fixation of the prosthesis.

The sequence of biological responses in bone healing in its broad sense may be outlined as follows:

A trauma elicits release of bone-derived growth factors from the bone matrix as well as other local growth factors from the surrounding tissue and the blood. These factors of which a number is known, some of which may b synthesized using ge-

netically modyfied organisms, elicits 1) an increased metabolism in the ar a, 2) changes of the secretion of superior hormones, and 3) a specific reaction leading to differentiation of primitive cells to form bone cells and proliferation of these. This specific reaction depends on the interaction between several polypeptide growth factors being dependant on hormones.

If it is desired to use such growth factors to stimulate the healing of bone fractures or healing of a bone and a prosthesis to be united with the bone, one could utilize systemic administration thereof. However, this route of administration is not desirable due to the high doses which must be used, both from an economical point of view and due to the considerable risc og undesired side effects due to systemic administration of biologically very potent substances in high doses.

Such substances could be administered locally to the broken bone or bone-prosthesis interface during an operation, optionally supplemented with later local injections. However, this implies that the substance applied should have a very high potency or may and be able to be kept in place for a sufficient time to carry out its function, and local injections are imprecise and increase the risk of infections.

It would also be possible to coat the prosthesis/osteosynthesis material with a vehicle which slowly releases the active substance or to add the active substance to bone cement. This approach is not convenient as the vehicle must not be toxic to the tissue, must not take up any substantial room which would leave a dead space on the surface and thus interfere with the healing. The slow release of the active substance(s) from a coating or a bone cement renders it very difficult to control the rate of release. Furthermore, the (passive) release of the active substance(s) or growth factor(s) from a vehicle or a bone cement would not make possible the admini-

stration of combinations of active substance(s) and/or growth factor(s) in a specific sequence.

Published International Patent Application No. WO89/03695 discloses a bone cement comprising a cell growth stimulant. In the specification it is mentioned that instead of mixing hGH with the cement, the hGH may be introduced to the bone-cement interface through a supplementary drainage tube which could be inserted to the cement. The purpose of the administration of hGH according to WO89/03695 is to stimulate the proliferation of bone cells into the cement phase in order to have an increased strength and there is no indication of carrying out the present invention, nor of obtaining the benefits thereof.

## BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to a method for local administration of a biologically active substance enhancing the healing of bone fractures or of a bone and a prosthesis to be united wherein the biologically active substance is administered directly to the bone surfaces to be healed or the interface between a bone and a prosthesis which are to be united.

It has now been shown, that administration of hGH during the healing of fractured bones or bone defects will speed up the healing giving a more rapid development of a firm cohesion between the surfaces to be united within the first weeks which is crucial to the healing.

It has also surprisingly been found that bone fractures in elderly individuals heal very rapidly when using the method of the invention.

According to ne aspect of the invention the biologically active compound is administered incorporated in a coating of a porous metal + hydroxyapatite on the surface of a prosthesis to be united with a bone.

According to the invention, the biologically active compounds may be administered by local injections which, however, may be somewhat troublesome to both the patient and the physician.

According to a a preferred second aspect of the invention, the biologically active substance is administered by continuous or pulsatile infusion to the bone surfaces or the interface between a bone and a prosthesis to be healed.

Continous or pulsatile infusion of the biologically active substance may, according to the invention be carried out as a real continous infusion using a continous pump to administer the substance to the surfaces to be healed, e.g. using an electrically controlled pump or an osmotic pump delivering a measured dosis of the substance over a sufficient span of time, preferably up to 3 weeks, more preferred up to from 1 1/2 to 2 1/2 weeks, or by several administrations given through a device forming part of the invention using a syringe or a pump capable of delivering an intermittent or pulsatile flow of the acitve substances.

However, the method of the invention may in certain cases be carried out as a systemic administration if it is judged to be appropriate by the physician considering the individual and state to be treated even though local administration is preferred.

Furthermore, the invention relates to a device for local administration of a biologically active substance enhancing the healing of bone fractures or of a bone and a prosthesis to be unit d, said device being in the form of a device stretching

acr ss or al ng the surfaces of bone or bone and prosthesis to be united and said device having apertures, communicating with an the internal hollow space, at or near the surfaces to be united.

The device of the invention may, according to a further aspect of the invention, be in the form of a hollow bone nail, fixation plate, screw or prosthesis having apertures leading to the surfaces to be united.

In accordance with a still further aspect of the invention the device is in the form of a hollow bone nail or fixation plate having apertures at the surface thereof at the level of the fractured bone to be healed.

According to yet another aspect of the invention the device is in the form of an artificial joint having a securing member having apertures at the surface thereof, said securing member being hollow or having internal canals communicating with the apertures.

A further aspect of the invention is constituted by an agent for use for local administration for enhancing the healing of bone fractures or a bone and a prosthesis to be healed, said agent comprising human growth hormone, thyroid hormone, antibiotic(s) and/or a local growth factor.

The substances to be used in the method of the invention may e.g. be human growth hormone (hGH), thyroid hormone and/or bone derived growth factors such as bone derived growth factor (BDGF) or human skeletal growth factor (hSGF), local regulators of bone metabolism, growth regulator hormones, bone proteins such as bone morphogenic protein (BMP), calcium-regulating hormones such as parathyroid hormone, Prostaglandin $E_2$, or growth stimulating factors such as insulin-like growth factor I (IGF-1) and insulin like growth factor II (IGF-II), colony stimulating factor (CSF), basic fibroblast

growth fact r (bFGF), plat let derived growth factor (PDGF), Factor XIII, transforming growth factor β (TGF-β), heparin binding growth factor, antibiotic(s) and/or epidermal growth factor (EGF).

Administration of antibiotics is of importance when exchanging alloplasts often being performed due to infections about an existing prosthesis. Infections are also often one of the factors eliciting pseudoarthroses. When administering antibiotics, the specific antibiotic(s) and the dosis regimen is determined by the physician in consideration of the individual and the specific infection to be treated and the severity thereof.

The bone fractures for which the present invention invention is especially advantageous are complicated fractures which need a rapid development of strength, fractures with delayed union or non-union as well as fractures in elderly people.

## BRIEF DESCRIPTION OF THE DRAWINGS

The invention is described more in detail below with reference to the drawings in which

Fig.1 shows cross sectional view of an embodiment of a bone nail according to the invention,

Fig.2 shows a general outline of a bone nail according to the invention located in the tibia of a rat,

Fig.3 shows a detail of a bone nail according to the invention,

Fig.4 shows a general outline of an embodiment of a hip joint prosthesis according to the invention,

Fig.5 shows a photo of a rat tibia comprising a nail,

Fig.6 shows a g neral outline of a fixation plate according to the invention, and

Fig.7 shows an X-ray picture of a rat having nail according to the invention in tibia and an osmotic pump

## DETAILED DESCRIPTION OF THE INVENTION

The bone nail shown in Fig.1 comprises a hollow member 1 being closed in one end 2. In the wall of the member 1 there are holes or apertures 3 communicating with the inner space 4 of the nail. The apertures 4 are preferably located evenly spaced at the circumference of the nail and preferably in a level corresponding to the fracture zone of the bone in which the nail has been inserted in order to secure the ends of the broken bone. A nail according to the invention may e.g. have 3 apertures located at the circumference. During the healing the biologically active substance(s) is (are) administered through the nail being introduced through the open end 5 of the nail, e.g. using a syringe or a pump, whereafter the substance diffuses through the apertures 4 and exercises its healing effect directly at the broken surfaces to be healed.

In Fig.2 the bone nail 1 is inserted in a tibia 6 of a rat. The tibia has a standard fracture 7 and the nail 5 is placed in such a manner that the apertures 3 are located at level with the fracture.

Reference is made to Fig.3 in which a photo shows a detail of a hole in a nail according to the invention. This embodiment has been made from a cannula being closed in the distant end and which has be n provided with holes using spark erosion

using tungsten wire in kerosene. The holes may also be made using laserdrilling as described in published International Patent Application No. WO89/0420.

An embodiment of a hip joint according to the invention is shown in Fig.4. The hip joint prosthesis comprises a head 8 and a securing member 9 to be secured to the femur. The securing member 9 has one or more canals 10 leading to apertures 3 at the surface of the securing member. The acetabular component 11 may also have one or more canal(s) 10 leading to apertures 3 at the surface to be united with the bone. The biologically active substances may be administered through the canals 10 to provide the local effect by diffusing through the apertures 3.

Fig.6 shows a fixation plate 12 according to the invention secured to a bone 13 having a fracture 14 using screws 15. The fixation plate 12 comprises canals 10 leading to apertures 3 at the surface of the fixation plate near the fracture to be healed. The fixation plate also comprises an adapter 16 communicating with the canals 10 for connecting a syringe or pump for administrring the biologically active substance(s).

Reference is made to fig.7 in which a photo shows an X-ray picture of a rat having a nail according to the invention placed in the broken tibia and an osmotic pump implanted under the skin at the back. The connecting polyethylene tubing is not visible on X-ray pictures.

The invention will be further described in the below Examples which are only to be considered as explaining the invention and not as limiting the invention, the scope of which is set forth in the appended claims.

**EXAMPLE 1**

**INCREASE OF THE STRENGTH OF INTACT BONES AND HEALING TIBIAL FRACTURES IN RAT (DUE TO ADMINISTRATION OF GROWTH HORMONE).**

The aim of the study was to investigate the influence of exogenous growth hormone administration on the biomechanical properties of healing diaphyseal fractures in the rat. In 90-day-old female Wistar rats a standardized tibial fracture was produced in the right tibia and non-rigid fixation was established using a K-wire as intramedullary nail. Two mg of biosynthetic human growth hormone (b-hGH) per kg body weight per day was given in 2 daily injections starting one week before fracture and continuing until testing. The control groups were injected with saline. After 40 days of fracture healing, the rats were killed and the fractured and the corresponding non-fractured bones were tested in a materials testing machine using a destructive three-point bending procedure. The results appear from the below Table I.

**Table 1**

Differences noted between growth hormone injected and controls after 40 days treating:

| Group | Max.load (N) | Stiffness (N/mm) | Max.stress ($N/mm^2$) |
|---|---|---|---|
| Control (n=8) | 21.9 ± 5.7 | 86 ± 39 | 15.3 ± 7.8 |
| + b-hGH (n=8) | 98.3 ± 8.3** | 365 ± 36* | 41.3 ± 8.6* |

Mean (S.E.M.); * $2p < 0.05$; ** $2p < 0.01$.

In the growth hormone injected animals, maximun load and stiffness f the intact bones had increased 40 days post fracture compared to the salin inject d controls, but there was no difference in terms of stress values, modulus of elasticity or normalized energy absorption.

In conclusion, growth hormone stimulates the mechanical strength development in healing diaphyseal fractures in the rat, when a total dose of 2 mg/kg BW/day is given in 2 daily injections. An increased strength observed in the non-fractured bones seems to be a quantitative phenomenon.

**EXAMPLE 2**

**THE INFLUENCE OF THE DOSIS OF GROWTH HORMONE ON FRACTURE HEALING IN THE RAT**

Growth hormone stimulates the proliferation of chondrocytes in vivo and in vitro. Growth hormone also stimulates weight gain and longitudinal bone growth depending on the dose and freqency of administration. Experimental fractures of long bones heal through a stage of cartilaginous callus if the mechanical conditions are not absolutely stable. The aim of the study was to investigate the effect of different doses of biosynthetic human growth hormone (b-hGH) on the mechanical strength development in healing experimental fractures.
In 90-day-old female Wistar rats, a closed fracture was produced by three-point bending 2 mm above the tibio-fibular junction in the right tibia. Closed medullary nailing was performed, and the bones were left to heal for 40 days. The rats were randomized into 6 groups: no injections, 0.9% NaCl (volume corresponding to b-hGH-treated groups), 0.08, 0.4, 2.0 and 10 mg b-hGH/kg/day given in 2 daily doses, starting one week prior to fracture and continuing until testing. Biomechanical testing was carried out in a materials testing

machine by a three-point bending pr cedure. Load and deformation was r corded continously, and maximum load, stiffness and energy absorption were calculated. The results appear from the below Table II.

**Table II**

Increased maximum load and stiffness of fractures treated with b-hGH in doses of 2 mg/kg/day and 10 mg/kg/day after 40 days healing as compared with controls:

| Treatment | n | Maximun load (N) | Stiffness (N/mm) |
|---|---|---|---|
| 1) no injections | 13 | 37.2 ± 6.5 | 171.0 ± 31.0 |
| 2) 0.9%NaCl | 14 | 30.2 ± 4.9 | 138.0 ± 24.2 |
| 3) b-hGH 0.08 mg/kg/day | 10 | 35.6 ± 8.2 | 166.0 ± 39.3 |
| 4) b-hGH 0.4 mg/kg/day | 15 | 34.9 ± 5.8 | 179.7 ± 30.5 |
| 5) b-hGH 2.0 mg/kg/day | 10 | 55.3 ± 10.2* | 219.9 ± 31.8* |
| 6) b-hGH 10 mg/kg/day | 13 | 69.3 ± 8.4** | 323.0 ± 30.0** |

Mean values ± SEM; * 2p < 0.05; ** 2p < 0.01

Conclusion: Biosynthetic human growth hormone administered twice a day accelerates the mechanical strength development in healing rat tibial fractures when given subcutaneously in doses of 2 mg/kg/day and 10 mg/kg/day.

**EXAMPLE 3**

**THE EFFECT OF GROWTH HORMONE ON DIFFERENT PHASES OF FRACTURE REPAIR IN THE RAT.**

The effect of growth hormone administration during different phases of fracture repair was investigated in a rat model.

Th biomechanical properties of healing tibial fractures was investigateed after 40 days of healing. Biosynthetic human gr wth horm ne (b-hGH), 2.7 mg/kg body weight/day was given in two daily injections to three groups of rats: (1) for the entire healing period, (2) for the first 20 days and (3) for the last 20 days of healing. Three corresponding groups of control rats were injected with saline. In group (1), maximum load and stiffness of the healing fractures increased to 165% and 175%, respectively, compared to the control group. In group (2), maximum load, stiffness, maximum stress, and energy absorption at ultimate load increased to 222%, 175%, 171%, and 247%, respectively, compared to the control group. In group (3), no statistically detectable effects were found. The results indicate: 1) that the stimulating effect of b-hGH on fracture healing is most pronounced during the first part of the healing period, 2) that no further effect will be obtained if the b-hGH administration is extended for the entire healing period, and 3) that pretreatment is not a prerequisite for obtaining a stimulating effect of b-hGH on fracture healing.

**EXAMPLE 4**

**THE INFLUENCE OF GROWTH HORMONE ON FRACTURE HEALING IN AGED RATS.**

It has been found that diaphyseal fractures in aged rats healed much slower than fractures in young adult rats. The present investigation was carried out in order to elucidate whether growth hormone influences the healing of tibial fractures in old rats, as it has been found that bone morphogenetic protein (BMP) is growth hormone dependent.

Two-year-old male Wistar rats were used for the experiment. A standardized tibial fracture was produced 2-4 mm above the tibiofibular junction and the fracture was stabilized with an intramedullary K-wire. The animals were rand mized for growth

hormone administration (2.7 mg b-hGH/kg/day in two daily injecti ns) or saline injections. Groups of animals w re terminat d and tested after 40 or 80 days of fracture healing. The results appear from the below Table III.

**Table III**

Effect of growth hormone (b-hGH, 2.7 mg/kg BW/day in two daily doses) on the mechanical properties of healing tibial fractures in 2-year-old rats:

| Experimental group | Ultimate load (N) | Stiffness (N/mm) | Ultimate stress $N/mm^2$) |
|---|---|---|---|
| 40 days healing control (n=12) | 16.3 ± 2.1 | 68.7 ± 25.3 | 10.20 ± 2.73 |
| 40 days healing b-hGH (n=13) | 21.0 ± 3.1 | 96.2 ± 26.6 | 11.33 ± 1.85 |
| 80 days healing control (n=12) | 48.01 ± 11.0 | 237 ± 60 | 36.5 ± 6.8 |
| 80 days healing b-hGH (n=11) | 85.4 ± 8.5** | 387 ± 33* | 57.7 ± 6.8 |

Mean values ± SEM; * $2p < 0.05$; ** $2p < 0.01$

Conclusion: The administration of growth hormone stimulates the mechanical strength development in healing tibial fractures in the aged rat.

**EXAMPLE 5**

**LOCAL ADMINISTRATION OF A LIQUID SUBSTANCE TO A FRACTURED BONE BY MEANS OF AN IMPLANTED MINIOSMOTIC PUMP AND A HOLLOW**

**INTRAMEDULLARY BONE NAIL HAVING APERTURES AT THE LEVEL OF THE FRACTURE.**

The feasibility of local administration of a liquid substance for a sufficient period of time to a fractured bone through a hollow bone nail having apertures communicating with the internal canal at the level of the facture has been investigated in an experimental model.

The bone nail was made from a stainless steel tube (a hypodermic needle) being closed at the tip by welding. At a distance of 9 mm from the free end of the needle, 3 circular holes spaced 120° and having a diameter of 70 µm were made by spark erosion using a tungsten wire in kerosene. Standardized fractures were made in the tibia of 4-month-old rats and the bone nails were inserted into the marrow cavity of the fractured tibiae and used for fixation of the fractures as shown i Fig.7. X-rays were taken to make sure that the apertures were localized at the level of the fractures. A miniosmotic pump manufactured by Alza Corp., California, U.S.A. (Alzet® 2ML4) was implanted under the skin at the back of the rats and connected to the bone nail by means of medical grade polyethylene tubing. The miniosmotic pumps contained 2 ml of saline and was capable of delivering a continous flow of 55 µl per day. The systems were tested for a period of 2 weeks. After removal of bone nails, tubing and pumps, the systems were examined under microscope: It was found that apertures were still open in all the bone nails and that the pumps were still capable of delivering the saline solution through the apertures.

CLAIMS

1. A method for local administration of biologically active substance(s) enhancing the healing of bone fractures or of a bone and a prosthesis to be united wherein the biologically active substance(s) is(are) administered directly to the bone surfaces to be healed or the interface between a bone and a prosthesis which are to be united.

2. A method as claimed in claim 1, wherein the biologically active substance(s) is(are) administered incorporated in a coating of a porous metal and hydroxyapatit on the surface of a prosthesis to be united with a bone.

3. A method as claimed in claim 1, wherein the biologically active substance(s) is(are) administered by continuous or pulsatile infusion to the bone surfaces or the interface between a bone and a prosthesis to be healed.

4. A device for local administration of a biologically active substance enhancing the healing of bone fractures or of a bone and a prosthesis to be united, said device being in the form of a device stretching across or along the surfaces of bone or bone and prosthesis to be united and said device having apertures, communicating with an internal hollow space, at or near the surfaces to be united.

5. A device as claimed in claim 4 being in the form of a hollow bone nail, fixation plate, screw, or prosthesis having apertures leading to the surfaces to be united.

6. A device as claimed in claim 5 being in the form of a hollow bone nail having apertures at the surface thereof at the level of the fractured bone to be healed.

7. A device as claimed in claim 5 being in the form of an artificial joint having a securing member having apertures at th surface thereof, said securing memb r being hollow or having internal canals communicating with the apertures.

AMENDED CLAIMS

[recived by the International Bureau on 18 June 1991 (18.06.91) ; original claims 5 and 6 cancelled ; original claims 1-4 amended ; claim 7 renumbered as claim 5 ( 1 page)]

1. A method for local administration of biologically active substance(s) enhancing the healing of a bone and a prosthesis to be united wherein the biologically active substance(s) is(are) administered directly to the interface between a bone and a prosthesis which are to be united.

2. A method as claimed in claim 1, wherein the biologically active substance(s) is(are) administered incorporated in a coating of a porous metal and hydroxyapatit on the surface of the prosthesis.

3. A method as claimed in claim 1, wherein the biologically active substance(s) is(are) administered by continuous or pulsatile infusion to the interface between a bone and a prosthesis to be healed.

4. A device for local administration of a biologically active substance enhancing the healing of a bone and a prosthesis to be united, said device being in the form of a prothesis having apertures, communicating with an internal hollow space, at or near the surfaces to be united.

5. A device as claimed in claim 4 being in the form of an artificial joint having a securing member having apertures at the surface thereof, said securing member being hollow or having internal canals communicating with the apertures.

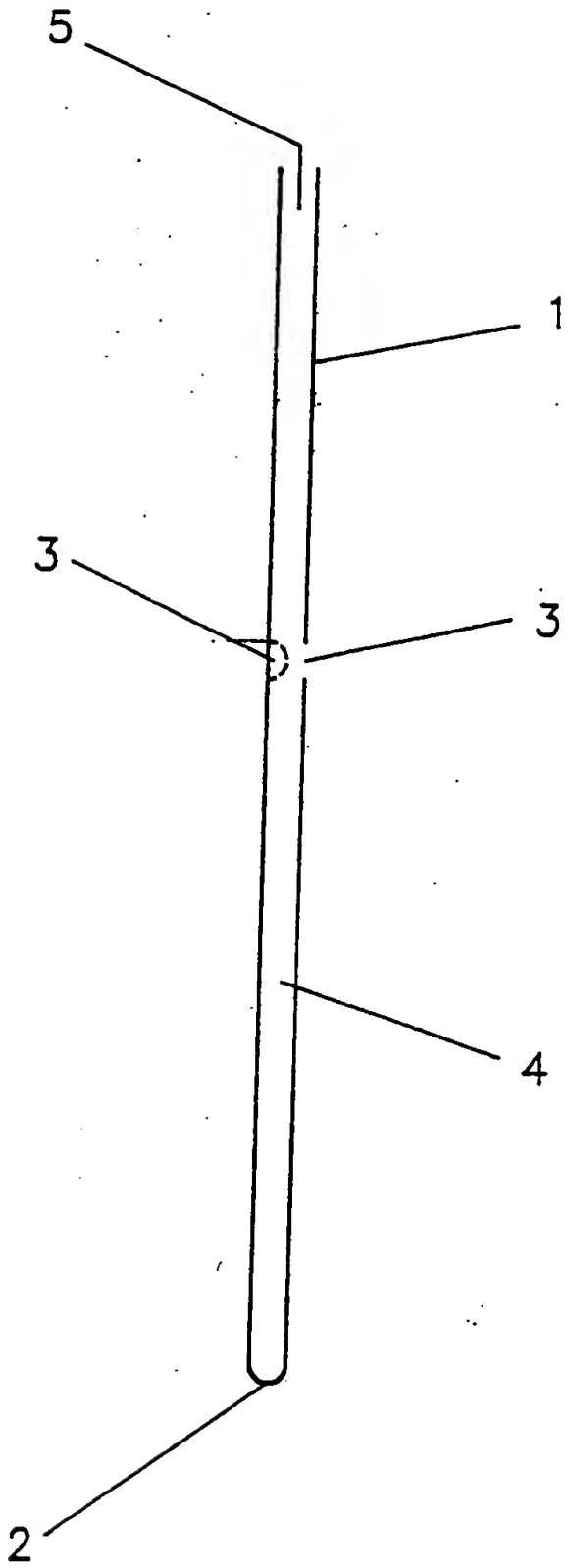


FIG. 1

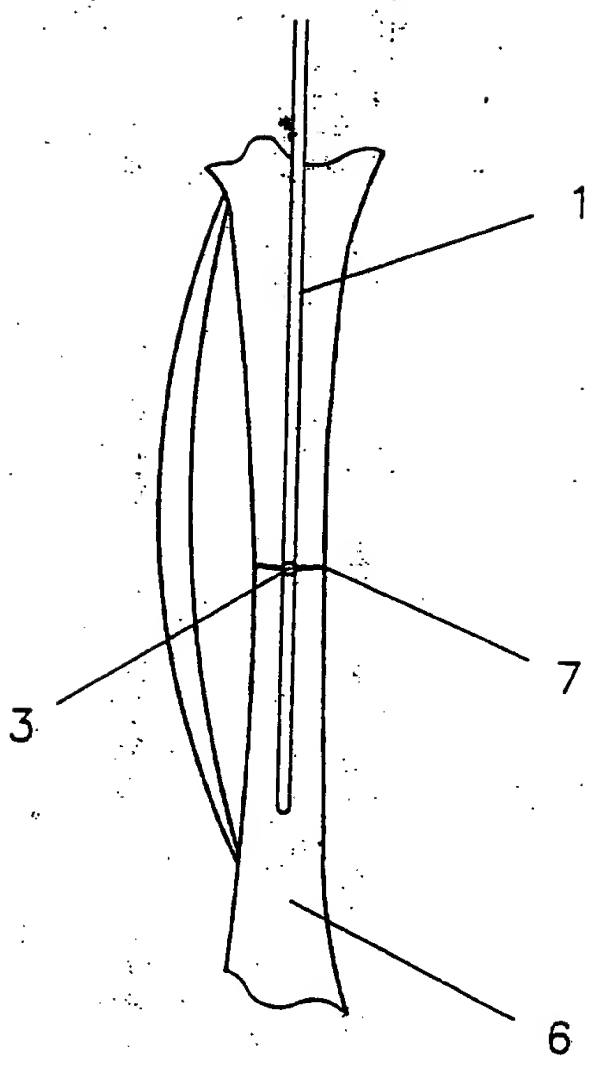


FIG. 2

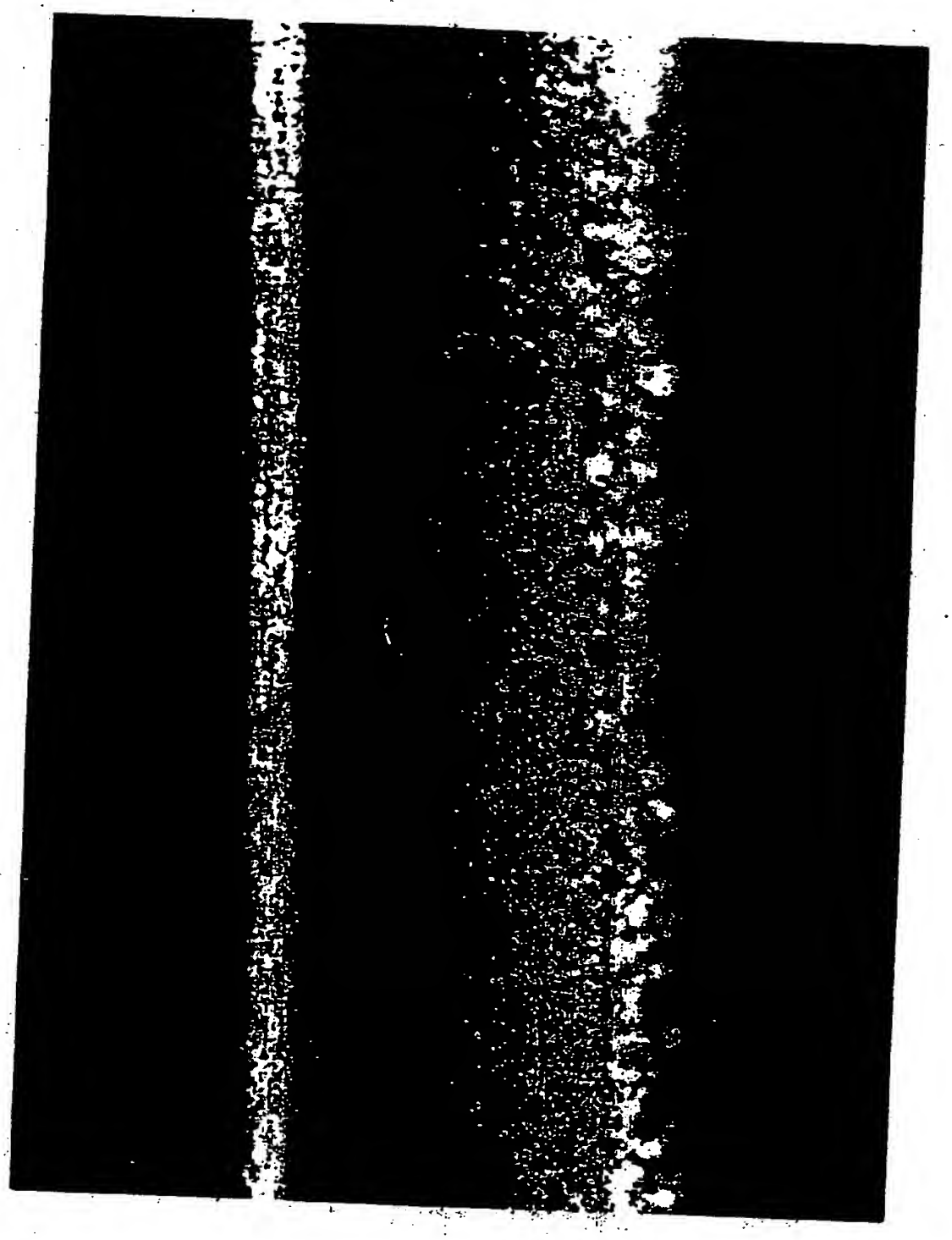

FIG. 3

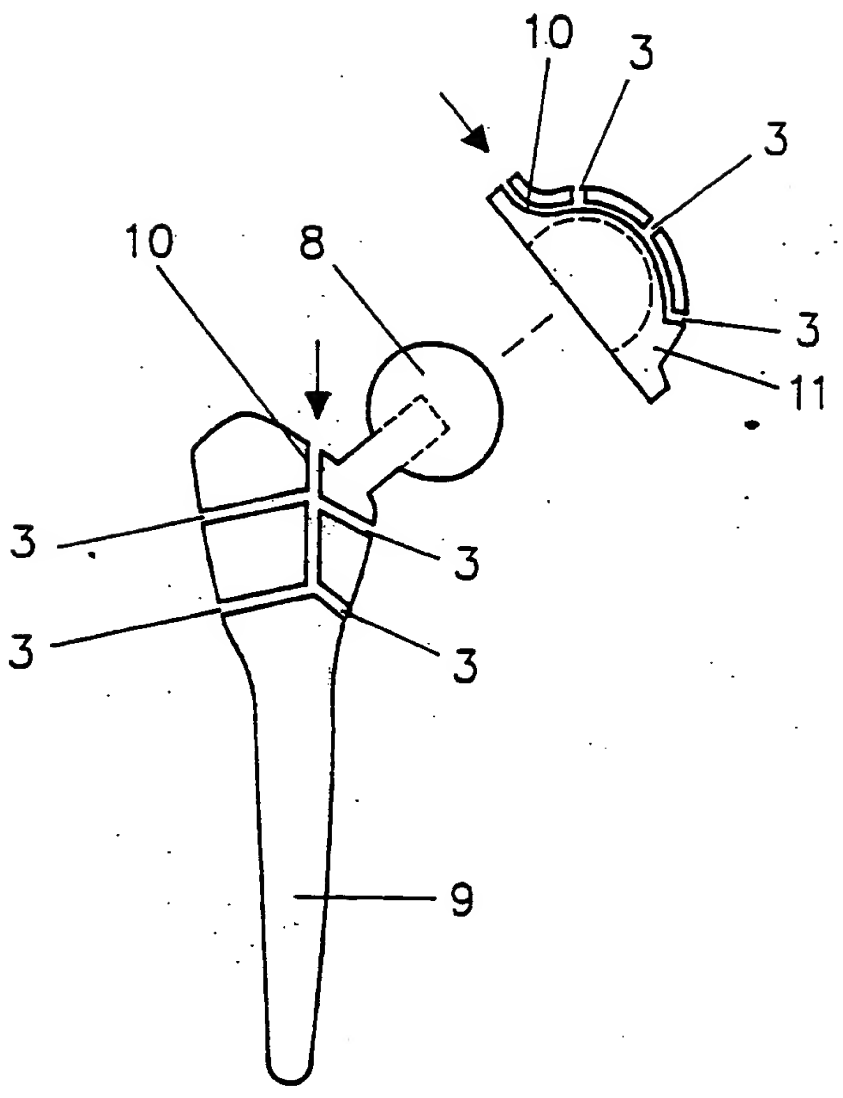


FIG. 4

FIG. 5

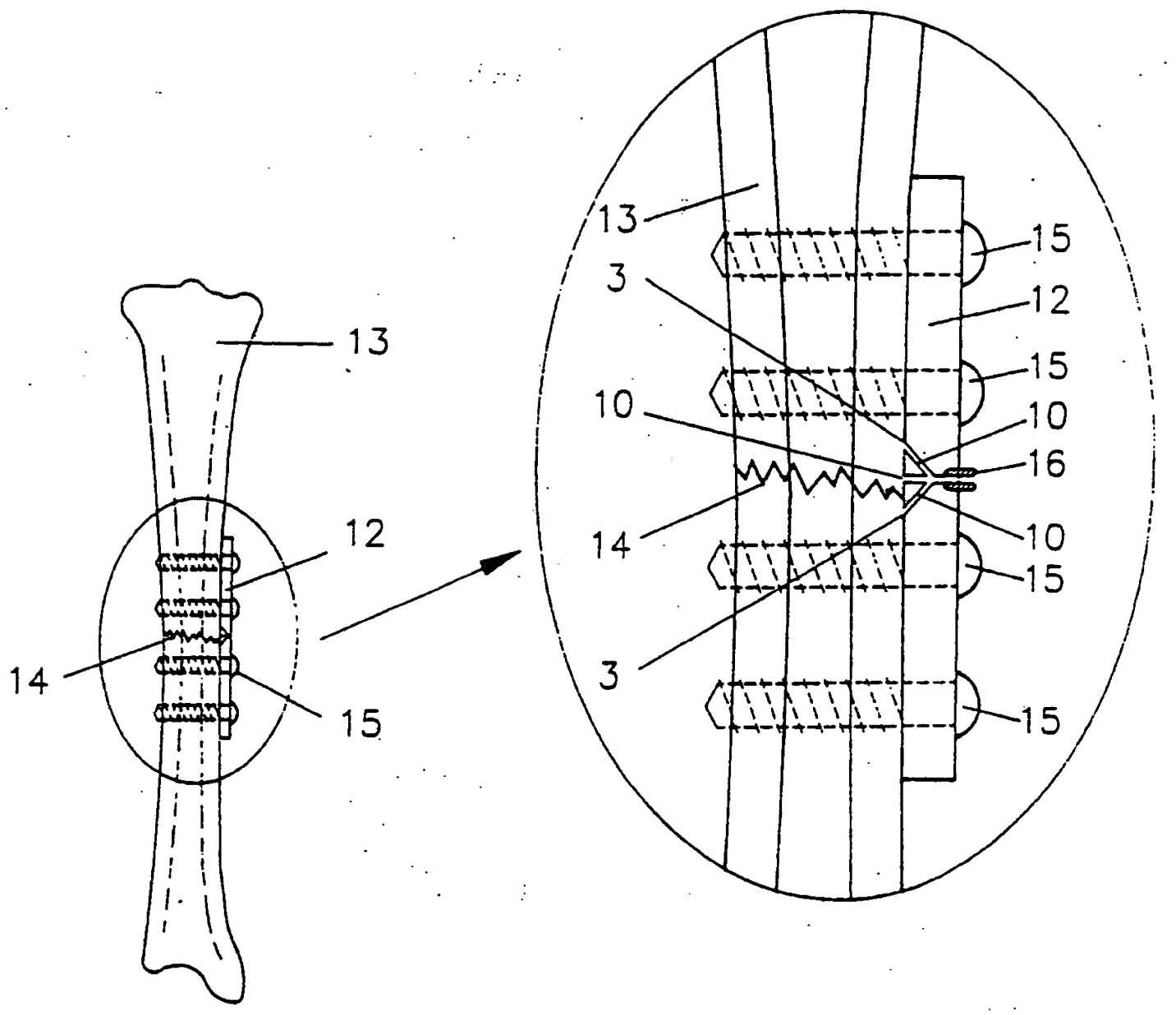


FIG. 6

FIG. 7

# INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 91/00022

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 B 17/58, A 61 L 25/00, A 61 L 27/00

## II. FIELDS SEARCHED

**Minimum Documentation Searched[7]**

| Classification System | Classification Symbols |
|---|---|
| IPC5 | A 61 B; A 61 F; A 61 L |

**Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]**

SE,DK,FI,NO classes as above

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category * | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| P,X | WO, A1, 9011726 (TSENTRALNY NAUCHNO-ISSLEDOVATELSKY INSTITUT TRAVMATOLOGII I ORTOPEDII) 18 October 1990, see the abstract and the figures -- | 4-7 |
| P,X | EP, A2, 0360139 (BOEHRINGER INGELHEIM KG) 28 March 1990, see the abstract, claim 7 and the figures -- | 4-7 |
| X | WO, A1, 8903695 (NORDISK GENTOFTE A/S) 5 May 1989, see page 4, line 31 - page 5, line 19; abstract; claims 1-13 -- | 4-7 |

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 7th May 1991 | 1991 -05- 15 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| SWEDISH PATENT OFFICE | Sofia Nikolopoulou<br>Sofia Nikolopoulou |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No |
|---|---|---|
| X | EP, A2, 0289314 (BRITISH BIO-TECHNOLOGY LIMITED) 2 November 1988, see page 9, line 7 - line 10; abstract; claims 1-11 -- | 4-7 |
| X | EP, A2, 0198213 (YEDA RESEARCH AND DEVELOPMENT COMPANY, LTD.) 22 October 1986, see column 2, line 41 - column 3, line 4; column 5, line 4 - line 10; abstract; claims 1-12 -- | 4-7 |
| X | WO, A1, 8701595 (BLÖMER, ALOIS) 26 March 1987, see abstract; claims 1-9 -- | 4-7 |
| X | EP, A2, 0149540 (ED. GEISTLICH SÖHNE A.G. FÜR CHEMISCHE INDUSTRIE) 24 July 1985, see page 8, line 32 - line 39; abstract -- | 4-7 |
| X | Derwent's abstract, No. 86-161 401/25, SU 1 192 796, publ. week 8625 (KHELIMSKII A M) -- | 4-7 |
| A | EP, A2, 0366029 (YAMAMURO, TAKAO) 2 May 1990, see the whole document -- | 4-7 |
| A | US, A, 4526909 (MARSHALL R. URIST) 2 July 1985, see the whole document -- | 4-7 |

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 1-3, because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/DK 91/00022

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 91-03-23 The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| WO-A1- 9011726 | 90-10-18 | NONE | | |
| EP-A2- 0360139 | 90-03-28 | DE-A- | 3831657 | 90-03-22 |
| | | JP-A- | 2121652 | 90-05-09 |
| WO-A1- 8903695 | 89-05-05 | AU-D- | 2616088 | 89-05-23 |
| | | EP-A- | 0386056 | 90-09-12 |
| EP-A2- 0289314 | 88-11-02 | NONE | | |
| EP-A2- 0198213 | 86-10-22 | AU-B- | 581735 | 89-03-02 |
| | | AU-D- | 5426186 | 86-09-18 |
| | | JP-A- | 61222452 | 86-10-02 |
| WO-A1- 8701595 | 87-03-26 | DE-A- | 3533369 | 87-03-19 |
| | | EP-A- | 0236468 | 87-09-16 |
| | | JP-T- | 63500917 | 88-04-07 |
| | | US-A- | 4863444 | 89-09-05 |
| EP-A2- 0149540 | 85-07-24 | JP-A- | 60227762 | 85-11-13 |
| | | US-A- | 4773406 | 88-09-27 |
| EP-A2- 0366029 | 90-05-02 | JP-A- | 2249556 | 90-10-05 |
| US-A- 4526909 | 85-07-02 | NONE | | |